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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KEI ROGER AOKI, MICHAEL W. GRAYSTON,
STEVEN R. CARLSON, and JUDITH M. LEON

Appeal 2009-010021[1]
Application 10/726,904
Technology Center 1600

Decided: May 21, 2010

Before ERIC GRIMES, TONI R. SCHEINER, and DONALD E. ADAMS, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 2, 4, 5, 29, 47, and 63, directed to a method for treating strabismus by administering the neurotoxic component of a botulinum toxin. The claims have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Heard May 4, 2010.

STATEMENT OF THE CASE

Claim 1 is representative of the subject matter on appeal:

1. A method for treating strabismus, the method comprising the step of administering to a patient a therapeutically effective amount of a neurotoxic component of a botulinum toxin to thereby treat strabismus wherein the neurotoxic component administered to the patient has a molecular weight of about 150 kilodaltons.

The Examiner relies on the following evidence:

Aoki et al.	US 6,113,915	Sep. 5, 2000
Aoki et al.	US 2001/0018415 A1	Aug. 30, 2001

Chun K. Tse et al., *Preparation and Characterisation of Homogeneous Neurotoxin Type A from Clostridium botulinum*, 122 EUR. J. BIOCHEM. 493-500 (1982).

Robert J. Balkan & Taylor Poole, *A Five-Year Analysis of Botulinum Toxin Type A Injections: Some unusual Features*, 23 ANN OPHTHALMOL 326-333 (1991).

Edward J. Schantz & Eric A. Johnson, *Properties and Use of Botulinum Toxin and Other Microbial Neurotoxins in Medicine*, 56 MICROBIOLOGICAL REVIEWS 80-99 (1992).

A. Kohl et al., *Comparison of the effect of botulinum toxin A (Botox ®) with the highly-purified neurotoxin (NT 201) in the extensor digitorum brevis muscle test*, 15(Suppl 3) MOV DISORD 165 (2000).

Sueng Han Han et al., *Effect of Botulinum Toxin A Chemodenervation in Sensory Strabismus*, 38 JOURNAL OF PEDIATRIC OPHTHALMOLOGY AND STRABISMUS 68-71 (2001).

Appellants rely on the following evidence:

Elizabeth Moyer & Paulette E. Setler, *Botulinum Toxin Type B: Experimental and Clinical Experience*, THERAPY WITH BOTULINUM TOXIN 71-85 (J. Jankovic et al., eds., 1994).

The claims stand rejected as follows:

Claims 1, 2, 4, 5, 29, 47, and 63 under 35 U.S.C. § 103(a) as unpatentable over Balkan or Han in view of Kohl, Tse, and Aoki '915.

Claims 1, 2, 4, 5, 29, 47, and 63 under 35 U.S.C. § 103(a) as unpatentable over Balkan or Han in view of Kohl, Aoki '915, and Aoki '415.

We affirm the first rejection, and reverse the second.

ISSUES

Has the Examiner established a reasonable basis for refusing to grant priority under 35 U.S.C. § 120 to parent application 08/173,996 on the grounds that the claims are not adequately enabled?

Has the Examiner established that treating strabismus by administering the neurotoxic component of a botulinum toxin, rather than a complexed form of the botulinum toxin, would have been obvious over the prior art?

FINDINGS OF FACT

FF1 The present Specification, under the heading "Background of the Invention," teaches that:

> [B]otulinum toxins, in particular botulinum toxin type A, have been used in the treatment of a number of neuromuscular disorders and conditions involving muscular spasm; for example, strabismus . . . The toxin binds rapidly and strongly to

> presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. This results in local paralysis and hence relaxation of the muscle afflicted by spasm.

(Spec. 1-2.) Nearly identical language appears in column 1 of US 6,974,578 B1 - the immediate parent of the present application and a continuation of abandoned parent application 08/173,996 (filed December 28, 1993).

FF2 The present Specification teaches that

> The neurotoxic component of a botulinum toxin has a molecular weight of about 150 kilodaltons and is thought to comprise a short polypeptide chain of about 50 kD which is considered to be responsible for the toxic properties of the toxin . . . and a larger polypeptide chain of about 100 kD which is believed to be necessary to enable the toxin to bind the presynaptic membrane.

(Spec. 3.) Nearly identical language appears in columns 1-2 of US 6,974,578 B1.

FF3 The neurotoxic component may exist in a dichain form, in which "short" and "long" chains are linked together by a disulfide bridge, or in the form of a single chain un-nicked protein (Spec. 3). This disclosure also appears in column 2 of US 6,794,578 B1.

FF4 According to the present Specification, "[b]oth the single and the dichain as well as the neurotoxic component are useful in the method of the present invention" (Spec. 3). Again, this language appears in column 2 of US 6,794,578 B1.

FF5 The present Specification discloses that "[a] patient with strabismus can be treated by injecting between about 1 to about 5 units of the neurotoxic component of a botulinum toxin type A free of or

substantially free of the botulinum toxin complex . . . into extraocular muscles . . . the amount injected varying based upon both the size of the muscle to be injected and the extent of muscle paralysis desired" (Spec. 23-24).

FF6 Schantz discusses the properties of botulinum toxins, including the purified neurotoxic component. According to Schantz:

> The nontoxic proteins bound to the neurotoxin apparently play an important role in maintaining the toxic shape of the neurotoxin. Careful handling of purified toxin is therefore important for maintenance of stability. Botulinum toxin type A is readily denatured by heat at temperatures above 40°C, particularly at alkaline pH. Solutions of the toxin lose toxicity when bubbles form at the air/liquid interface causing stretching and pulling of the neurotoxin out of its toxic shape. This denaturation also takes place in an atmosphere of nitrogen or carbon dioxide. Dilution to extremely low concentrations (nanograms per milliliter) also tends to decrease the stability of the neurotoxin, but this can be prevented by diluting with a buffered solution (at pH 6.8 or below) containing another protein such as gelatin and certain albumins such as bovine or human serum albumin. When the pH is raised above 7.3, the neurotoxin is liberated, which is very labile. Because of its lability the neurotoxin is not practical for medical applications.

(Schantz 82, col. 2 (internal citations omitted).)

> Most recent information concerning the structure and pharmacology of botulinum toxin has been obtained with purified neurotoxins, but it is unlikely that these will be used in a clinical setting. The toxin complexes are much more stable than neurotoxins and can be diluted and formulated with retention of toxicity. Pure neurotoxins can be kept for several weeks to months in solution in the cold but are inactivated on dilution, formulation, and drying.

(*Id.* at 89, col. 2.)

FF7 Schantz teaches that purified botulinum neurotoxins "have high specific toxicities" (Schantz 87, col. 2), and are capable of producing paralysis in rats (*id.* at 89, col. 2).

FF8 Balkan discloses treating strabismus in humans with injections of complexed botulinum toxin type A (Balkan, abstract).

FF9 Tse describes purification and characterization of the neurotoxic component of type A botulinum toxin (Tse 494).

FF10 According to Tse, "[w]hen this neurotoxin . . . was injected into rat hind-leg muscle, it produced local paralysis within 24 h" (Tse 498, col. 1). In addition, "[a]s clearly demonstrated with impure neurotoxin complexes, pure neurotoxin specifically and characteristically inhibited stimulated and spontaneous release of acetylcholine at the vertebrate neuromuscular junction" (*id.* at 499, col. 2 (internal citations omitted)).

FF11 According to Moyer, "[r]elatively few studies have been reported evaluating the in vivo muscle paralytic potency of BTX [botulinum toxin] types other than type A. Usually, these studies have been performed using rats, a species apparently particularly resistant to type B toxin" (Moyer 76), unlike guinea pigs, which are equally susceptible to type A and type B toxins. "In rats, no toxin studied [including type E and type F] has been found to be as potent as type A" (*id.*).

FF12 Appellants note that Moyer concluded that "given the species-specificity of the various toxin types, rodent studies must be considered inconclusive with respect to predicting the relative clinical potency of the various types of BTX" (Moyer 76; App. Br. 16).

PRINCIPLES OF LAW

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223 (CCPA 1971).

"Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace. Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003).

ANALYSIS

The Examiner rejected the claims as obvious over the combined teachings of Balkan or Han in view of Kohl, Tse, and Aoki '915. In addition, the Examiner rejected the claims as obvious over the combined teachings of Balkan, Han, Kohl, Aoki '915, and Aoki '415.

According to Appellants, the Han and Kohl references, published in 2001 and 2000 respectively, the Aoki '915 patent, filed in 1999, and the Aoki patent application publication '415, published in 2001, "are not prior art with regard to the pending claims" (App. Br. 14, 18) because "the claims are entitled to priority to the December 28, 1993 filing date" of their parent application 08/173,996 (*id.*).

The Specification teaches that the neurotoxic component of botulinum toxin is useful in treating strabismus (FF4, FF5). However, the Examiner concluded that the claims were not enabled by parent application 08/173,996 - largely on the basis of Schantz's assessment that the neurotoxic component of botulinum toxin is not practical for medical applications because of its lability (Ans. 6). As framed by the Examiner, "[t]he question was not whether one could make or isolate the purified toxin but whether one could use it in a clinical setting" (*id.* at 20). According to the Examiner, "[t]he specification did not disclose methods that one of ordinary skill in the art could utilize to render the pure toxin clinically effective . . . [and] [w]ithout such guidance, one would be burdened with undue experimentation to practice the claimed invention" (*id.* at 7).

We disagree with the Examiner's rationale for denying the present claims priority to the parent application. Rather than establishing that the use of the neurotoxic component of botulinum toxin would have required undue experimentation, the evidence relied on by the Examiner merely establishes that one of skill in the art would have expected the 150 kilodalton neurotoxic component of botulinum toxin to be less convenient to administer to a patient in a clinical setting than the complexed form of the toxin. In any case, the claims aren't limited to a "clinical setting." Moreover, the Examiner has essentially dismissed evidence that the purified neurotoxin, despite being more labile than the complexed toxin, had been shown to exert effects comparable to the complexed toxin in animal studies (FF7, FF10).

Accordingly, we agree with Appellants that the Han and Kohl references, published in 2001 and 2000 respectively, the Aoki '915 patent,

filed in 1999, and the Aoki '415 publication, published in 2001, "are not prior art with regard to the pending claims" (App. Br. 14).

Nevertheless, we conclude that the claimed invention is unpatentable over Balkan and Tse, the remaining prior art references relied on by the Examiner. The Examiner found that Balkan "teaches the administration of botulinum toxin type A and type F for the treatment of strabismus" (Ans. 9), and that Tse teaches that pure neurotoxin produces paralysis in rat muscles, and inhibits release of acetylcholine at the vertebrate neuromuscular junction, just like the corresponding complexed neurotoxin (*id*). We agree with the Examiner's conclusion that "it would have been obvious to one of ordinary skill [in] the art to use pure neurotoxin for the treatment of strabismus because [Tse teaches that] pure neurotoxin has similar activity in the paralysis of muscles as complexed neurotoxin and has similar activity against spontaneous release of actetylcholine" (*id.* at 10).

Appellants contend that Balkan "relate[s] to the injection of complexed botulinum toxin into a human muscle for treating strabismus" (App. Br. 15), while Tse "relates to rat muscles" (*id.* at 16). Appellants contend that one of ordinary skill in the art wouldn't combine Balkan and Tse because Moyer provides evidence that "the effects of the neurotoxic component on mouse muscles cannot be applied to human muscles" (*id.*). Similarly, Appellants contend that Balkan "relate[s] to methods for clinical treatment of strabismus in humans . . . [while] the teachings of the Tse reference relate to improved vaccines and probes" (*id.*). Appellants contend that "[t]he use of a compound as a drug for treating strabismus in humans is very different from the use of that compound as an antigen or a probe, and the practice of the two methods may be entirely incompatible" (*id.*).

Appellants' arguments are not persuasive. Balkan teaches that injections of complexed botulinum toxin type A can be used to treat strabismus (FF8). Tse teaches that complexed toxin type A and the neurotoxic component of type A have comparable activities *in vivo*, in that both "specifically and characteristically inhibited stimulated and spontaneous release of acetylcholine at the vertebrate neuromuscular junction" (Tse 499; FF10). The fact that Moyer shows that different botulinum toxin types exhibit different species-specificities (e.g., rats are resistant to type B, while guinea pigs aren't (FF11)) has no bearing on whether one would expect a given complexed toxin and its corresponding purified neurotoxin to exhibit similar activities in the same animal.

Finally, the fact that Tse suggests that "purified neurotoxin could provide a superior and novel vaccine . . . to raise immunoglobulins for therapeutic use and for development of immunoassays for the toxin in clinical specimens and foodstuffs" and that it "could be an invaluable probe for nerve membrane component(s)" (Tse 493, col. 2) has no bearing on one whether would expect a given complexed toxin and its corresponding purified neurotoxin to exhibit similar activities *in vivo*.

CONCLUSIONS OF LAW

The Examiner has not established a reasonable basis for refusing to grant priority under 35 U.S.C. § 120 to parent application 08/173,996 on the grounds that the claims are not adequately enabled. Accordingly, the Han, Kohl, Aoki '915, and Aoki '415 references do not qualify as prior art with respect to the claims on appeal.

Nevertheless, the Examiner has established that treating strabismus by administering the neurotoxic component of a botulinum toxin, rather than a complexed form of the botulinum toxin, would have been obvious over the combined teachings of Balkan and Tse.

The rejection of claims 1, 2, 4, 5, 29, 47, and 63 under 35 U.S.C. § 103(a) as unpatentable over Balkan and Tse is affirmed.

The rejection of claims 1, 2, 4, 5, 29, 47, and 63 under 35 U.S.C. § 103(a) as unpatentable over Balkan alone is reversed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

alw

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